**REMARKS**

Claims 1-19, 21, 31, 32, 41-43, 52, 53 and 57-61 were pending in the subject application. By this Amendment, applicants have amended claims 1, 12, 16 and 58-61.

**Restriction**

In the June 6, 2005 Office Action, the Examiner withdrew claims 19, 21, 32, 41, 43 and 52 from further consideration under 37 U.S.C. §1.142(b) and made the restriction requirement "final". The Examiner noted applicants' assertion that no process of manufacturing the claimed pharmaceutical composition has been cited, and referred applicants to U.S. Patent No. 6,407,079 to Muller et al. The Examiner then alleged that Muller et al. disclose a method of producing pharmaceutical compositions comprising a sparingly water-soluble drug (citing Abstract and claim 18).

In response to the Examiner's citation of Muller et al., applicants respectfully point out that Muller et al. does not disclose a process for making the pharmaceutical composition as claimed in Group I. Indeed, Muller et al. cannot possibly so disclose because the pharmaceutical composition of Group I is novel. Furthermore, even if one, for a reason which remains unspecified in the current record, were to attempt to make the claimed composition using the disclosure of Muller et al., there's no reasonable expectation that the process of Muller et al. would work.

Therefore, the Examiner's restriction of Group III from Group I remains unsupported. Under M.P.E.P. §806.5(f), the burden falls upon the Examiner to provide an example of a materially different process by which a restricted product can be made. The Examiner has not cited such a process, as the Examiner cannot in view of the novelty of the claimed product. Furthermore, the mere hindsight allegation that the process of Muller et al. "can" be attempted

without an indication of whether it would work, does not satisfy M.P.E.P. §806.05(f). Therefore, the restriction of the process claims of Group III from the product claims of Group I is improper.

Similarly, the Examiner's restriction of claim 19 from the Group I claims is unsupported. Under M.P.E.P. §806.5(h), the burden falls upon the Examiner to provide an example of a materially different product with which the claimed method of using can be practiced. The Examiner cited steroids. However, it is self-evident that claim 19 depends on, and requires the use of, the compound of claim 1, not some other product. It is also clear that claim 19 encompasses use of the compound of claim 1 with a steroid, but not of a steroid alone. Thus, claim 19 always requires the use of at least the compound of claim 1. Even if use of a steroid alone could be use of a materially different product, claim 19 cannot be practiced with a steroid alone but requires the use of the compound of claim 1. Therefore, the restriction of the sole claim to a method of using from the claims to the product being used of Group I is improper.

If the restriction requirement is maintained contrary to M.P.E.P. §§806.05(f) and (h), then applicants request rejoinder of method of use claim 19 and process of making claims 21, 32, 41, 43, and 52, pursuant to 37 C.F.R. §1.141(b), once elected product claims 1-18, 31, 42, 53, and 57-61 are deemed allowable.

**Petition from Requirement for Restriction Under 37 C.F.R. § 1.144**

If the Examiner continues to maintain the restriction requirement of Group I from Groups II and III in contravention of M.P.E.P. §§806.05(f) and (h), and further contrary to 37 C.F.R. §1.141(b), applicants request that the above discussion and applicants' September 24, 2004 reply to the restriction requirement be considered a Petition to the Commissioner to review the requirement for restriction under 37 CFR § 1.144.

**Claim Objections**

In sections 5-8 of the June 6, 2005 Office Action, the Examiner required correction of claims 1, 12, 16 and 59-61. Specifically, the Examiner required that "composition" in the last phrase suggest the claim state "pharmaceutical composition" as recited in the preamble of the claims.

In response, applicants appreciate the Examiner's careful review of the claims and have amended claims 1, 12, 16 and 59-61 to correct the informality. Accordingly, applicants respectfully request that the Examiner withdraw this objection to the claims.

**Double Patenting**

In sections 9 and 10 of the June 6, 2005 Official Action, the Examiner provisionally rejected claims 1-18, 31, 42, 53 and 57-61 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-13, 24, 25, 37, 48 and 52 of copending Application No. 10/758,397 (U.S. Patent Application Publication 2005/0008634 A1). The Examiner alleged that the conflicting claims are not patently distinct from each other.

In response, applicants defer discussion of the provisional rejection until copending Application No. 10/758,397 issues, or until the obviousness-type double patenting rejection is the only rejection remaining in the present application. M.P.E.P. §804(I)(B)

**Rejection Under 35 U.S.C. §112**

In sections 12 and 13 of the June 6, 2005 Official Action, the Examiner alleged that claims 31, 42, 53 and 58 are indefinite for failing to particularly point out and claim the subject matter of the invention. Specifically, the Examiner noted that claims 31, 42 and 53 depend on withdrawn process claims, and questioned what

amount is predetermined in claim 58.

In response, without conceding the correctness of the Examiner's position, applicants have amended claim 58 to no longer recite "a predetermined amount of".

With respect to claims 31, 42 and 53, applicants point out that they are entitled to claim their inventive product in any proper form, including in the form of "product-by-process" claims. M.P.E.P. §2173.05(p). Claims 31, 42 and 53 are product-by-process claims. Applicants are also entitled to incorporate into claim 31, 42 and 53 the limitations of other pending claims by reference. M.P.E.P. §2173.05(f). The process claims to which claims 31, 42 and 53 refer are still pending, albeit improperly withdrawn in the June 6, 2005 Office Action. Therefore, no ambiguity exists as to the subject matter of claims 31, 42 and 53.

Accordingly, the rejection of claim 31, 42 and 53 under 35 U.S.C. §112, second paragraph, is improper and should be withdrawn.

**Rejections Under 35 U.S.C. §103**

Mozes in view of the '856 patent

In sections 15 and 16 of the June 6, 2005 Office Action, the Examiner alleged that claims 1-4, 7, 8, 11 and 31 are unpatentable over U.S. Patent Application Publication No. 2004/0127408 A1 to Mozes ("Mozes") in view of U.S. Patent No. 5,997,856 to Hora et al. ("the '856 patent"). The Examiner alleged that Mozes discloses: peptides and pharmaceutical compositions for the treatment of systemic lupus erythematosus; a 19-mer peptide sequence identified as SEQ ID NO: 6, which has 100% identity with current application SEQ ID NO: 1; the salt of the peptide, including an acetate salt; and a pharmaceutical composition comprising the peptide and a

pharmaceutically acceptable carrier. The Examiner acknowledged that Mozes does not explicitly disclose a pharmaceutical composition comprising a pharmaceutically acceptable salt of a peptide and a substituted β-cyclodextrin.

The Examiner alleged that the '856 patent discloses: the solubilization and/or stabilization of polypeptides, especially proteins, using cyclodextrin selected from the group consisting of hydroxypropyl, hydroxyethyl, glucosyl, maltosyl, and maltotriosyl derivatives of β-cyclodextrin; protein, hydroxypropyl β-cyclodextrin compositions that have proteins at concentrations ranging from 0.25 mg/ml to 1 mg/ml; and a lyophilized composition comprising a polypeptide and a stabilizing/solubilizing amount of cyclodextrin selected from the group consisting of hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β-cyclodextrin.

The Examiner alleged that one would have been motivated to manufacture the pharmaceutical composition comprising an aqueous carrier, a pharmaceutically acceptable salt of the peptide disclosed by Mozes with the β-cyclodextrin derivatives disclosed by the '856 patent, because of the enhanced solubilization and stabilization of the peptide in the β-cyclodextrin derivative solution. The Examiner further alleged that it would have been obvious to the person having ordinary skill in the art to manufacture the pharmaceutical composition comprising an aqueous carrier, a pharmaceutical acceptable salt of the peptide identified as SEQ ID NO: 1 that is disclosed by Mozes, along with the β-cyclodextrin derivatives disclosed by the '856 patent to treat systemic lupus erythematosus. The Examiner further alleged that it would have been obvious to the person having ordinary skill in the art to lyophilize the composition comprising the peptide disclosed by Mozes, and the β-cyclodextrin derivatives disclosed by the '856

patent, on the basis that the '856 patent discloses a lyophilized polypeptide/β-cyclodextrin composition.

Applicants' Reply

In response, applicants maintain that the present invention is patentable over Mozes in view of the '856 patent for reasons that follow.

*Mozes*

Mozes discloses synthetic human peptides of at least 12 and at most 30 amino acid residues. (Abstract) No solubility problems are disclosed as being associated with any of the peptides in Mozes. Furthermore, Mozes makes no reference or even remotely suggest that there is a need to improve the solubility of salt forms of the peptides. Mozes also does not mention cyclodextrins, much less a β-cyclodextrin for solubilization of the specific peptide salt (Compound 1) of the present invention.

*'856 patent*

The '856 patent discloses a method and compositions for solubilization of polypeptides, especially proteins. The '856 patent defines polypeptides as amino acid polymers containing more than 20 peptide linkages (21 amino acids) and proteins as very large polypeptides (column 12, lines 58-61). The '856 patent distinguishes polypeptides from oligopeptides, which have between 2-20 peptide linkages (3-21 amino acids)(column 12, lines 59-61).

The '856 patent focuses on solubilization of polypeptide proteins, not on solubilization of peptides. The '856 patent does not even acknowledge that the solubilization of peptides or of peptide salts is a problem. Peptide salts, such as Compound 1 of the present

invention, are not even mentioned in the '856 patent. The '856 patent also does not exemplify solubilization of a peptide, or of a peptide salt. Furthermore, the '856 patent does not teach use of sulfobutylether-β-cyclodextrin.

*Motivation to combine Mozes and the '856 patent is lacking*

There exists no motivation to combine Mozes and the '856 patent. First, as noted above, Mozes discloses small peptides whereas the '856 patent provides a solubilization method targeting very large polypeptides; and neither Mozes nor the '856 patent show a peptide salt as recited in the pending claims. As such, the Examiner's stated rationale for combining the two references does not apply.

Second, and more importantly, Mozes does not identify that solubility is a problem with any of its peptides. Mozes mentions salts on page 7, paragraph 0088, as something that can be used to "modify" solubility of the peptide. Applicants' claims recite a salt of a peptide. From the disclosure of Mozes, the solubility of a salt of its peptides, and certainly of a salt thereof, would appear satisfactory. The peptides are in fact used in the examples of Mozes without any apparent solubility problem.

Thus, absent hindsight, there is no reason of record motivating the combination of the salt of the peptide of Mozes with any solubility enhancer, much less the ones of the '856 patent. This deficiency alone makes the obviousness rejection improper.

*Motivation to select a β-cyclodextrin from all known solubility enhancers is lacking*

Even if solubility of Compound 1 was known to be a problem, there is no reason of record to select a β-cyclodextrin from the large number of known solubility enhancers. The two β-cyclodextrins used to solubilize Compound 1 are but two members among panoply of available solubility enhancers. Absent hindsight, there is no motivation in the current record to select a β-cyclodextrin. In fact, applicants tried numerous solubility enhancers before finding that β-cyclodextrin can be used (see Table 1, page 27 of the Specification).

This deficiency alone makes the obviousness rejection improper.

*Even if Mozes and the '856 patent are combined, there is no expectation of success*

Even in the absence of the required motivation but to explore hindsight, applicants contend that nothing more than an "obvious to try" rationale has been presented in support of the rejection of record. Specifically, assuming the record did contain a motivation to manufacture a pharmaceutical composition (comprising an aqueous carrier, a pharmaceutically acceptable salt of the peptide and β-cyclodextrin derivatives), one skilled in the art would have no expectation that doing so would result in a composition having improved solubility.

An obviousness analysis requires taking into consideration whether or not one of ordinary skill in the art would have an expectation of success. M.P.E.P. §2144.08. "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (emphasis added).

Applicants have described the difficulty of selecting an appropriate solubility enhancer to improve the solubility of the claimed peptide salt on page 24, line 21 to page 27, line 6 of the subject application. Applicants summarize testing of a variety of solubility enhancers, most of which were unsuccessful. Only after significant development and testing could an appropriate solubility enhancer be selected to improve the solubility of Compound 1. Certainly one could not have expected success with a β-cyclodextrin before such testing.

Nothing in the current record supports the Examiner's assertion that a β-cyclodextrin should be selected from the large number of known solubility enhancers. This deficiency alone makes the obviousness rejection improper.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes and the '856 patent.

Mozes in view of the '856 patent and Anderson et al.

In section 17 of the June 6, 2005 Official Action, the Examiner alleged that claims 5 and 6 are unpatentable over Mozes in view of the '856 patent as applied to claims 1-4, 7, 8, 11, 31, 42, 53, 57 and 59-61 and in further view of Anderson, B.D. and Flora, K.P. (Chapter 34, pages 739-754, *The Practice of Medicinal Chemistry*, edited by Camilles Georges Wermuth, Academic Press 1996). The Examiner acknowledged that Mozes and the '856 patent do not explicitly disclose a pharmaceutical composition having a pH between 6.5 and 8.5. However, the Examiner alleged that Anderson et al. disclose the ideal pH for injectable formulations to be the pH of blood, 7.4, while pH above 9 causes tissue necrosis, and pH below 3 causes extreme pain and phlebitis. The Examiner alleged

that one would have been motivated to manufacture a pharmaceutical composition within the range of pH being between 6.5 and 8.5 to be able to administer an injectable pharmaceutical composition.

Applicants' Reply

In response, applicants point out that this rejection suffers from the same deficiencies as the rejection based on Mozes in view of the '856 patent. Anderson et al. fails to remedy any of the deficiencies noted above.

Furthermore, Anderson et al. offer nothing of relevance for formulating a pharmaceutical composition containing Compound 1 at physiological pH. As summarized on page 24, line 21 to page 25, line 26 of the specification, many solubility enhancers were tested to improve solubility of Compound 1. However, none of the solubility enhancers achieved adequate solubility at physiological pH. Solubility was only reached at pH levels below 3 and above 9 (Specification page 24, lines 27-28). Not until applicants used a β-cyclodextrin was solubility of Compound 1 improved at physiological pH.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes, the '856 patent and Anderson et al.

Mozes in view of the '856 patent and the '127 patent

In section 18 of the June 6, 2005 Office Action, the Examiner alleged that claims 9, 10 and 12-18 are unpatentable over Mozes in view of the '856 patent as applied to claims 1-4, 7, 8, 11 and 31 and further in view of U.S. Patent No. 5,134,127 to Stella et al. ("the '127 patent"). The Examiner acknowledged that Mozes and the '856 patent do not disclose a pharmaceutical composition comprising a sulfobutyl ether substituted β-cyclodextrin. However, the

Examiner alleged that the '127 patent discloses the use of sulfoalkyl ether cyclodextrin derivatives as solubilizing agents for water insoluble drugs for oral, intranasal, or parenteral administration, and the use of sulfobutyl ether substituted β-cyclodextrin complexed to digoxin, progesterone, testosterone, and phenytoin. The Examiner alleged that one would have been motivated to manufacture the pharmaceutical composition comprising an aqueous carrier, a pharmaceutical acceptable salt of the peptide disclosed by Mozes with the sulfobutyl ether substituted β-cyclodextrin derivatives disclosed by the '127 patent.

Applicants' Reply

In response, applicants point out that this rejection suffers from the same deficiencies as the rejection based on Mozes in view of the '856 patent. The '127 patent fails to remedy any of the deficiencies noted above.

Furthermore, the '127 patent offers nothing of relevance for the solubilization of Compound 1. The '127 patent discloses use of sulfoalkyl ether cyclodextrin derivatives as solubilizing agents for water insoluble small molecule drugs for parenteral administration, not peptides. The '127 patent does not even mention peptides or proteins, much less exemplify their solubilization. As such, there is no suggestion or motivation to modify or combine the '127 patent with Mozes or the '856 patent

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection based on Mozes, the '856 patent and the '127 patent.

**Summary**

In view of the remarks made herein, applicants respectfully request that the Examiner reconsider and withdraw the rejections made to the claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.

No fee other than the enclosed $120.00 fee for one-month extension is deemed necessary in connection with the filing of this response. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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